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REVIEW

Circulating Tumor DNA as Biomarkers for Cancer Detection

Xiao Han [1,2,a], **Junyun Wang** [1,b], **Yingli Sun** [1,*,c]

[1] *CAS Key Laboratory of Genomic and Precision Medicine, China Gastrointestinal Cancer Research Center, Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100101, China*
[2] *University of Chinese Academy of Sciences, Beijing 100049, China*

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Abstract Detection of **circulating tumor DNAs** (ctDNAs) in cancer patients is an important component of cancer **precision medicine** ctDNAs. Compared to the traditional physical and biochemical methods, blood-based ctDNA detection offers a non-invasive and easily accessible way for cancer diagnosis, prognostic determination, and guidance for treatment. While studies on this topic are currently underway, clinical translation of ctDNA detection in various types of cancers has been attracting much attention, due to the great potential of ctDNA as blood-based **biomarkers** for early diagnosis and treatment of cancers. ctDNAs are detected and tracked primarily based on tumor-related genetic and epigenetic alterations. In this article, we reviewed the available studies on ctDNA detection and described the representative methods. We also discussed the current understanding of ctDNAs in cancer patients and their availability as potential **biomarkers** for clinical purposes. Considering the progress made and challenges involved in accurate detection of specific **cell-free nucleic acids**, ctDNAs hold promise to serve as **biomarkers** for cancer patients, and further validation is needed prior to their broad clinical use.

Introduction

Over 8.2 million people die of cancer each year due to the inaccessibility of appropriate detection procedures and treatments [1]. Researchers have been exploring methods for the detection and cure of cancers via cancer screening, prognostic determination, and monitoring. However, up till now, there are no known diagnostic methods that do not hurt the physical health of patients during the process of cancer detection. For example, radiology is extensively used in cancer detection, but excessive ionizing radiation could pose potential health risk to the examined patient [2,3]. On the other hand, non-radiation modalities, such as ultrasound scans and magnetic resonance imaging (MRI) scans, are thought to be inefficient for the detection of minimal residual disease [4–6]. Furthermore, the "solid biopsy" method of detection is invasive, and cannot accurately track dynamic changes in

* Corresponding author.
E-mail: sunyl@big.ac.cn (Sun Y).
[a] ORCID: 0000-0001-9262-7254.
[b] ORCID: 0000-0003-0573-7856.
[c] ORCID: 0000-0002-8401-5554.

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tumors due to tumor heterogeneity [7–9]. Thus, developing non-invasive and precise methods for the early diagnoses of cancers is an increasingly urgent requirement in the era of precision medicine (PM).

Liquid biopsy is a type of technique for sampling and analyzing of non-solid biological tissues, mainly used in disease diagnosis [10]. Circulating tumor DNAs (ctDNAs), being a popular class of liquid biopsy biomarkers, are believed to be easily detected in the plasma of cancer patients even in the early stages of their disease [11–13]. ctDNAs display considerable variations in DNA sequences. Moreover, tumor-specific DNA methylations can also be consistently measured and reflected within ctDNAs, showing the potential for wide application in clinical detection of cancers [14–18]. To provide an overview of current utilities of clinical therapy and potential biomarkers, we summarized the methods of detection that are frequently used nowadays, such as imaging-based methods [19–21] and solid biopsies [22–25] in **Table 1**. Biomarkers that are currently in use or under investigation in liquid biopsies are also shown in the table, including proteins [26–28], circulating tumor cells (CTCs) [7,11,29], ctDNAs [10,30,31], circulating cell-free RNAs [32–34], and exosomes [35–37]. In this article, we mainly discuss several new methods for using ctDNAs and ctDNA methylations in the early detection of cancers. The challenges and potential applications of ctDNA detection are also discussed in this review.

Profiles of ctDNAs and CTCs

On January 9, 2016, the Chinese Academy of Sciences (CAS) announced its precision medicine initiative (CASPMI). This initiative aims to establish a new medical paradigm characterized by high-efficiency and low-cost disease diagnoses and treatments of individual patients, based on their genetic and epigenetic composition. In this program, some studies would focus on the risks of occurrence of cancers and other major chronic diseases for early warning signs and interventions. Performing liquid biopsies, specifically by capturing CTCs and ctDNAs in the plasma or serum of cancer patients, is an ideal strategy for clinical utility in the PM research programs [38,39].

For around 1000 years, biopsies have been used clinically for the diagnoses, management, and planning the treatments of diseases [10]. Given the many obstacles in sequentially obtaining repeated biopsies, including the inconvenience to the patients, the potential surgical complications, and the clinical risks, clinical use of multi-site biopsies is often impractical [22–25]. As an alternate, liquid biopsies are currently being used to address the temporal and spatial heterogeneity in solid tumors. Liquid biopsies could even be used in cancer detection, thus facilitating early diagnoses and treatments [10,40–42].

CTCs are shed into the bloodstream by primary tumors during early tumorigenesis [43]. They can be purified from blood, and separated from normal blood cells by the differences in their physicochemical characteristics [43]. Ashworth demonstrated the presence of CTCs in 1869 [44], but their value was overlooked until the 1990s [29]. The CTCs have immense potential for cancer detection and management of advanced disease, as reported in cases of breast cancers, prostate cancers, and colorectal cancers [45–47]. However, it is difficult to identify and isolate CTCs since they are present in circulation at the rate of only one CTC per 1×10^9 normal blood cells in patients with metastatic cancers [48]. Many

Table 1 Comparison of different cancer detection methods for their clinical utilities

Detection method		Strengths	Limitations	Refs.
Imaging-based methods (CT, MRI, PET, *etc.*)		Rapid; easy to use; displaying solid tumor visually	Unable to detect minimal residual disease; exposing patients to additional ionizing radiation	[19–21]
Solid biopsy		Reflecting certain histological issues; short operating time	Unable to represent the entre tumor due to the intra- and inter-tumor heterogeneity; serial biopsy often impractical; discomfort suffered by the patient; not accessible for some tumors	[22–25]
Liquid biopsy	Protein (CA-125, CEA, PSA, *etc.*)	Non-invasive; easy to obtain	Low specificity; Unable to be detected in vast majority of patients with advanced cancers	[26–28]
	CTCs	Non-invasive; high specificity; demonstrating colocalization of signals; evaluating protein expression; potentially addressing tumor heterogeneity	Low signal-to-noise; affected by heterogeneity on selection methods	[7,11,29]
	ctDNA	Non-invasive; high specificity and sensitivity; providing personalized snapshot of disease; fully representing tumors	Low signal-to-noise; lack of colocalization, protein expression, and functional studies	[10,30,31]
	Circulating cfRNA	Non-invasive; stable; demonstrating distinct gene expression patterns from particular tumor	Lack of large-scale studies; lack of correlations between tumor behavior and findings	[32–34]
	Exosomes	Non-invasive; stable within exosomes; easy to isolate or enrich	Lack of large-scale studies; hard to define	[35–37]

Note: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; CA-125, carcinoma antigen-125; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; cfRNA, cell-free RNA.